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Hematologic Neoplasia and the Central Nervous System

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Central nervous system (CNS) involvement with malignant cells is a well recognized complication of hematologic neoplasms. A number of disorders such as acute lymphoblastic leukemia and high grade lymphoma frequently involve the CNS and prophylactic therapy is advised. Disorders such as acute myeloid leukemia (AML) and multiple myeloma are less likely to be associated with CNS involvement. This series describes three cases of CNS involvement by malignant hematologic disease: myelomatous meningitis, CNS chloromas complicating AML, and primary lymphomatous meningitis. Am. J. Hematol. 62:234–238, 1999.

Key words: meningeal; lymphoma; leukemia; myeloma

INTRODUCTION

The development of leptomeningeal infiltration with malignant cells is a well-recognized complication of many hematologic neoplasms. In disorders such as acute lymphoblastic leukemia and high-grade lymphoma, central nervous system (CNS) involvement is so common that prophylactic therapy is usually utilized. In other hematologic neoplasms, CNS involvement is well described but not typically as a presenting feature, or rarely occurs at any time in the clinical course. The three cases presented here demonstrate unusual CNS manifestations of distinct hematologic neoplasms.

CASE 1: MYELOMATOUS MENINGITIS

Case Description

The patient is a 69-year-old male who was diagnosed with multiple myeloma in 1994. He presented with lytic bone disease in the femur, and the diagnosis of multiple myeloma was made following an orthopedic stabilization procedure. He had predominantly light chain disease and was initially treated with eight cycles of melphalan and prednisone with a good response. Eight months after treatment, there was an increase in light chain excretion and he was restarted on melphalan and prednisone, then cytoxan and predisone, again with a good response. After an additional 8 months off therapy, he developed bone pain and a marked increase in light chain excretion, prompting initiation of a Vincristine–Adriamycin–Decadron (VAD) regimen and local radiation therapy. Just prior to the fifth cycle, he developed acute left-sided weakness with focal seizure activity and fever, for which he was hospitalized. Lumbar puncture showed a protein of 214 mg/dl and 12 nucleated cells/ml, predominantly plasma cells, some of which were multinucleated or immature. (Fig. 1). Magnetic resonance imaging (MRI) showed multiple lytic lesions in the cranium, no lesions in the brain or leptomeninges, and a soft tissue abnormality in the left side of the sphenoid sinus. Our clinical impression was myelomatous involvement of the leptomeninges secondary to skull lesions. He received radiation to the base of the skull and remained stable for 4 weeks, but died from progressive myeloma 8 weeks after this presentation.

Discussion

Although neurologic complications of multiple myeloma are common, they usually represent extensions

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Case 1: Myelomatous Meningitis (1500X)

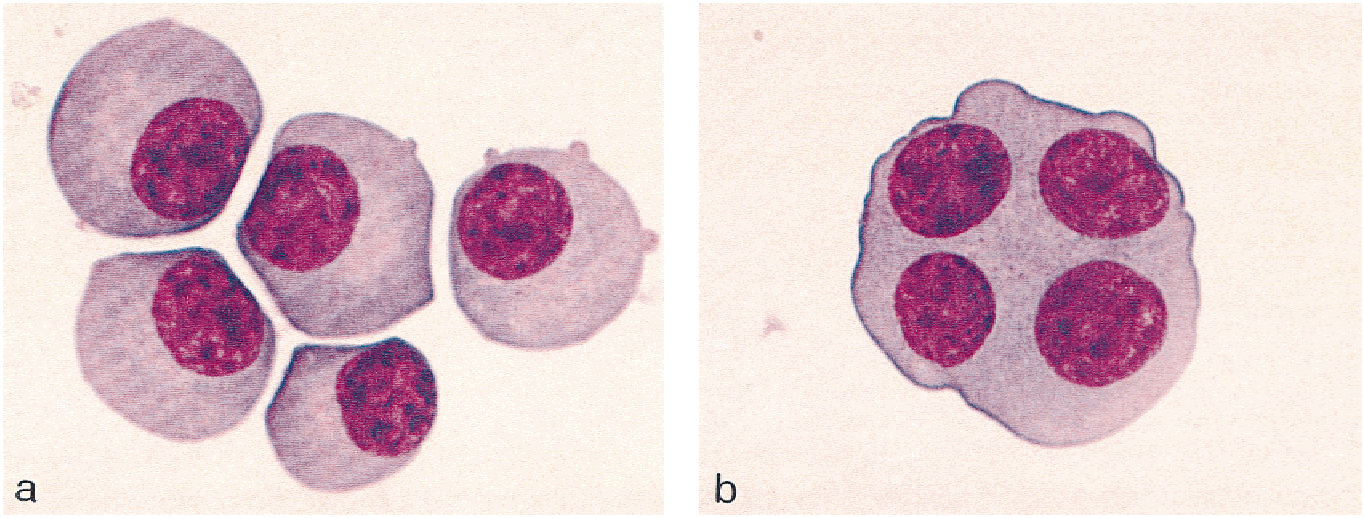

Fig. 1

Case 2: Lymphomatous Meningitis (1500X)

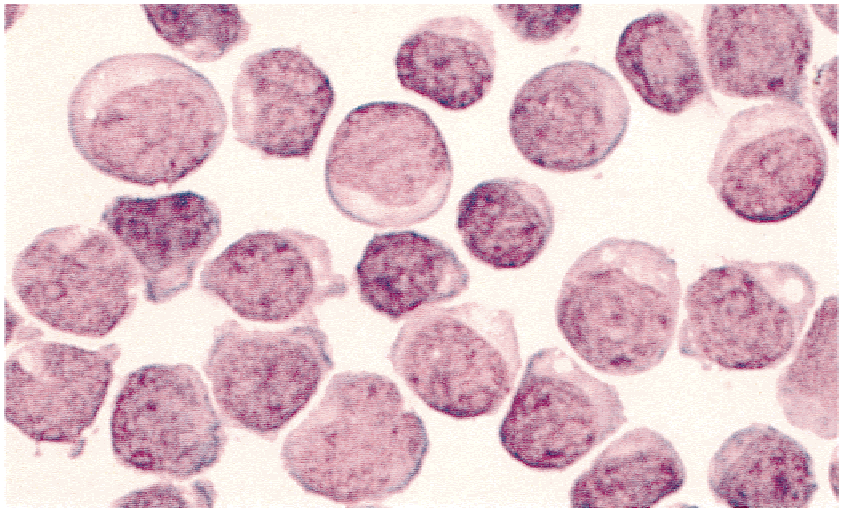

Fig. 2

Case 3: Intracranial Granulocytic Sarcomas (1500x and 600X)

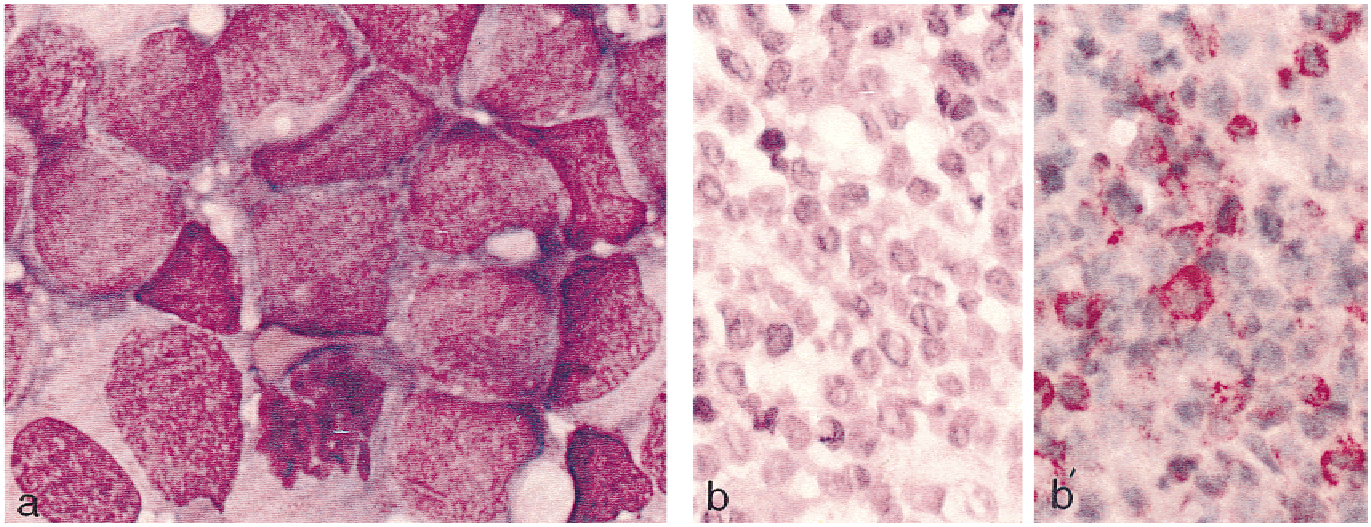

Fig. 3

Figures 1, 2, and 3. Legend on overleaf.

from bony disease that cause local nerve compression or neuropathy associated with a paraprotein. Leptomeningeal infiltration with myeloma cells or myelomatous meningitis is exceedingly rare. When it occurs, it is likely the result of hematogenous spread or infiltration from contiguous structures. This case demonstrates an unusual manifestion of myeloma, namely, leptomeningeal plasma cell infiltration presenting with neurologic signs and symptoms.

On the basis of radiologic and cytologic observations, reports of meningeal myeloma have generally concluded that this complication usually develops during the final stage of the disease and that only palliative treatment is indicated [1–4]. However, response to treatment may occur and careful examination of the cerebrospinal fluid for plasma cells in patients with myeloma and neurologic symptoms is prudent. In the patients reviewed by Leifer et al. in 1992 [4], leptomeningeal myeloma usually presented with mental status changes, occasionally with meningeal signs, and was more common in patients with plasma cell leukemia, and patients with IgA and IgD myeloma. The median time between diagnosis and neurologic symptoms was nine months (range 1 month to 5 years). After treatment with intrathecal and/or systemic chemotherapy or radiation therapy the median survival is quite short, 5 months in "responders" and only 1 month in others.

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CASE 2: LYMPHOMATOUS MENINGITIS

Case Description

A 31-year-old man with insulin-dependent diabetes mellitus and hypertension was admitted with a 2-month history of diplopia, progressive cranial nerve palsies and intermittent bifrontal headache. Outpatient examination 6 weeks prior to hospitalization documented a left sixth nerve palsy, and the glycosylated hemoglobin was elevated. Magnetic resonance imaging without gadolinium and magnetic resonance angiography were normal. Symptoms were considered to be ischemic or diabetic retinopathy, but improved blood pressure and diabetic control induced no significant change in symptoms. Three weeks before admission he developed gait dysequilibrium, right-sided ptosis, supraorbital headache and emesis and the next week he noted numbness on the right side of his mouth, slurred speech, and difficulty eating.

The patient was first diagnosed with diabetes mellitus 9 years earlier, and he had had at least three episodes of hypoglycemia complicated by seizures. His medications included captopril, hydrochlorothiazide, insulin, and prednisone. There was no history of cigarette, alcohol, drug use, or risk behavior for HIV infection and no family history of malignancy or immune deficiency states. On neurologic examination at admission, the pupils were equal and reactive with a prominent right efferent defect. There was a complete right third nerve palsy and a dense right seventh nerve palsy (lower motor neuron type) with intact sensation. The left sixth nerve palsy previously noted had nearly resolved. Funduscopic exam was normal as was visual acuity. Gait and coordination were intact although he tended to fall backward on Romberg testing. Deep tendon reflexes were decreased in the upper extremities and normal in the lower extremities. Laboratory data included a nonreactive serum RPR, erythrocyte sedimentation rate 12 mm/h, negative ANA, negative HIV test, and nonelevated cryptococcal antibody titer. He was started on prednisone for possible Bell's palsy. Lumbar puncture the following day showed 68 nucleated cells/l, 25% of which had clefted nuclei with prominent nucleoli (Fig. 2).

On physical examination he was well-nourished, in no distress and vital signs were normal. There was no icterus, lymphadenopathy, or abdominal organomegaly. The neurologic exam was as described above. Cell marker studies on repeat LP showed mostly T-cells of the phenotype CD2+/CD3−/CD7+/CD4+/CD8+/CD1a+, a pattern which is characteristic of the thymocyte stage of

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Fig. 1. (a) Cytocentrifuge preparation of CSF stained with Wright–Giemsa (1500×) showing aggregate of well-differentiated plasma cells. (b) Multinucleated plasma cell, CSF, Wright–Giemsa.
Fig. 2. Cytocentrifuge preparation of CSF stained with Wright–Giemsa (1500×) showing numerous, somewhat pleomorphic, immature lymphoid cells with high N/C ratios (but varying amounts of cytoplasm), immature chromatin, some nuclear clefting, and some cells with prominent nucleoli.
Fig. 3. (a) Imprint of the biopsy stained with Wright–Giemsa (1500×). Although many of the cells are blasts, others show evidence of granulocytic maturation. (b, b′) Brain biopsy stained with H & E (600×) showing infiltration by abnormal monomorphic immature cells, many of which are Leder positive (chloroacetate esterase) indicating their granulocytic origin (b′).

immature T-cell differentiation and a diagnosis of T-cell lymphoblastic lymphoma. The bone marrow was normocellular with normal maturation of all three cell lines, a mild increase in eosinophils and unremarkable flow cytometric studies.

The patient was treated with prednisone (100 mg/day), intravenous cytosine arabinoside (3 gm/m^2 every 12 h for 6 doses), and intrathecal cytosine arabinosine (50 mg each week for 3 weeks). Seven days after the start of systemic chemotherapy, the nucleated cell count in the cerebrospinal fluid decreased to 2 cells/mm^3 and there was gradual improvement in cranial nerve function. He also received radiation to the base of the brain (3,000 cGy), another course of cytosine arabinoside for 6 doses and maintenance therapy for 6 months. He developed vertebral osteomyelitis requiring prolonged antibiotics and one year later, his disease relapsed with both bone marrow and CNS involvement. He received an allogeneic bone marrow transplant from a matched unrelated donor, but died of transplant-related complications 3 months later.

Discussion

The diagnosis of leptomeningeal lymphoma may be difficult when the patient presents with meningoencephalitis or polyneuropathy in a clinical setting suggestive of a viral or postviral syndrome. In our patient, diabetic neuropathy was the leading clinical diagnosis. A rigorous search for systemic involvement including imaging studies and bone marrow examination with flow cytometric analysis revealed no evidence of systemic lymphoma. Cytologic examination of CSF revealed suspicious lymphoid cells, but the diagnosis was definitively confirmed only by flow cytometric analysis which revealed a population of T-cells with an immature phenotype characteristic of T-cell lymphoblastic lymphoma.

Primary malignant lymphoma of the central nervous system is rare and accounts for only 2% of extranodal lymphomas [1,2]. The incidence of primary CNS lymphoma has risen in the last 2 decades at least in part due to HIV infection and drug-induced immunosuppression. Most cases are B-cell lymphomas that present with parenchymal mass lesions. Leptomeningeal involvement may occur as a late complication in some patients with systemic non-Hodgkin's lymphoma, particularly in those with aggressive (large-cell) histology, but primary involvement of the leptomeninges is extremely rare and accounts for only 7.6% of all primary CNS lymphomas [3]. Many cases of primary leptomeningeal lymphoma never progress to systemic disease, suggesting that this is a distinct disease entity [3].

Some lymphomas of T-cell origin have a predilection for CNS involvement [4–6]. Involvement of the CNS is found in 15–50% of patients with lymphoblastic lymphoma and can occur at initial presentation or during relapse. Lymphoblastic lymphoma with an exclusively leptomeningeal presentation is extremely rare, with only one other reported case in the literature [3].

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CASE 3: INTRACRANIAL GRANULOCYTIC SARCOMAS

Case Description

The patient was a 70-year-old male who presented with a 3–4 week history of lethargy, fatigue, and dyspnea. On admission, the total white blood cell count was 220,000/μl, hematocrit was 34%, and the platelet count 54,000/μl. Virtually all of the nucleated cells were myeloblasts. A bone marrow was consistent with the M4 subtype of acute, nonlymphoid leukemia, which was confirmed by the presence of both myeloid and monocytic markers noted on flow cytometry. His karyotype was normal. He underwent leukopheresis followed by induction chemotherapy with mitoxantrone plus ARA-C and the nadir bone marrow showed no blasts. Consolidation treatment consisted of two cycles of high dose ARA-C at 5 and 12 weeks, with prolonged thrombocytopenia (50,000–70,000/μl), but no evident increase in marrow blasts. Eight weeks after the second cycle of ARA-C consolidation he developed a headache and blurred vision and a CT scan revealed numerous enhancing lesions throughout the brain in both hemispheres (Fig. 4). A brain biopsy demonstrated granulocytic sarcoma within the cerebral cortex (Fig. 3).

Discussion

Extramedullary acute leukemia is a feature of 2–14% of acute leukemias [1–3], typically of myeloid origin. In fact, the greenish tint that these tumors exhibit grossly ("chloromas") is attributed to the myeloperoxidase produced by myeloid cells [1,2]. Usually chloromas are

Fig. 4. Contrast enhanced CT scan of the head. Multiple enhancing lesions in both hemispheres.

found in bone, skin, periosteum, soft tissue, and lymph nodes, but they can occur in virtually any anatomic site, including mediastinum and pleura and the genitourinary and gastrointestinal organs. The first reports date to over 175 years ago, but it was only in the last 20 years that intraparenchymal involvement such as occurred in our case was recognized [3].

From the handful (about 15) of cases with intracranial involvement to date the following generalizations are plausible.

- Female predominance [4] in distinction from chloromas involving other sites.
- Occurrence *usually* months-to-years after complete remission, as opposed to occurrence upon initial presentation of the acute leukemia. This implies hematogenous implantation with subsequent tumor growth unaffected by chemotherapy agents that do not penetrate the blood–brain barrier [4]. In contrast, meningeal acute leukemia occurs as the result of CNS infiltration of the dura and subarachnoid space by leukemic cells that traverse superficial arachnoidal veins and adventitia. Since this sequence does not appear to be the pathway leading to intraparenchymal chloromas, the role of prophylactic intrathecal chemotherapy at the time of initial presentation of AML is not certain. Since high-dose cytosine arabinoside penetrates the blood-brain barrier, its widespread use for consolidation has seemingly precluded the need for prophylactic intrathecal or cranial radiation therapy in AML.
- The unenhanced CT scan usually shows hyperdense lesions, while enhancement shows the lesions to be circumscribed, homogeneous with or without a relatively hypodense center [9]. The CT radiographic differential diagnosis is short: meningioma versus solid tumor metastases.
- The magnetic resonance scan [5,8] demonstrates the lesions to be hypotense to isotense on both T1-weighted and T2-weighted images, characteristics that would not occur with abscess or hemorrhage. Meningiomas and solid tumors occasionally can be isotense but the former characteristically has calcification and increased bone formation as opposed to bony destruction. There is marked homogenous enhancement after the administration of contrast.
- Radiation of intraparenchymal chloroma is the modality of choice as chloromas usually are highly radiosensitive even at 10–20 Gy, but surgical decompression has been applied in patients with large masses within the brain parenchyma [4]. Ultimately, the outcome will depend upon response at the underlying leukemia, and in our case, marrow relapse occurred.

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